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some clinical outcomes that have clinical relevance in their own right and to identify potential indicators of harm alteration that could be obtained much sooner after the introduction of PREPs than would be possible when evaluating heart disease and cancer.

Other candidate diseases for such evaluation might include periodontal disease and Crohn's disease. Here the outcomes to assess would be the effects of various conventional tobacco products and PREPs on the natural history of the condition, including intermittancy, progression or regression, and longitudinally collected biomarkers of disease severity. As noted above, PREPs that alter the history and outcomes of these conditions could be further evaluated for specific constituent exposures that are associated with this altered history. This may lead to a more refined understanding of pathogenic mechanisms as well.

There is also room for clinical and basic research on intermediate clinical outcomes. For example, as noted in this chapter, the risk of osteoporosis has also been strongly linked to cigarette smoking. In controlled observational studies, bone mineral density has been found to be significantly lower among cigarette smokers, which contributes to a higher risk of osteoporotic fractures among older populations. While the effects of smoking on fracture rates may take a few decades or longer to detect, it is possible that surveillance for bone mineral density among those using PREPs and conventional products may prove valuable in a shorter time period and thus serve to detect important outcomes over an interval in which tobacco policy and clinical preventive interventions may have their greatest effects.

preeclampsia among smokers but also found that smokers who did develop preeclampsia tended to have worse pregnancy outcomes. In a case-control study by Marcoux et al. (1989), the protective effect of smoking for preeclampsia was maintained only among pregnant smokers who continued to smoke throughout pregnancy or quit after 20 weeks' gestation. The postulated mechanisms for this protective effect of cigarette smoking includes the nicotine-mediated inhibition of fetal thromboxane A, stimulation of NO production, increased levels of thiocyanate, endothelial damage secondary to the oxidative stress effect of cigarette smoke, and altered immune responses (reviewed in Lindqvist and Marsal, 1999; Conde-Agudelo et al., 1999; Cnattingius et al., 1997).

SUMMARY

Several important diseases and conditions of adults, in addition to cardiovascular disease, chronic obstructive pulmonary disease, and various cancers, have been associated with tobacco use. Some of the associations are supported by substantial scientific evidence, and a causal linkage is likely. These illnesses must ultimately be subjected to the same evaluation with regard to changing risks and outcomes associated with potential reduced-exposure products (PREPs), because they are common and clinically important, even if not often as fatal as the diseases considered earlier in this report. Further, each of the conditions for which the association with tobacco use is substantial also offers the opportunity to address pathogenic mechanisms related to the varying constituents of PREPs, as well as the impact on disease incidence of coordinated behaviors and exposures such as alcohol use, various dietary elements, and certain medications.

RECOMMENDATIONS

Surveillance

The committee recommends that selected conditions, reviewed in this chapter, be part of a comprehensive, population-based surveillance program, as outlined in Chapter 6. This will allow determination of trends in occurrence for these tobacco-related conditions and assessment on a national basis of whether changes in tobacco product use have an effect on these important health problems. Based on surveillance findings, more specific population, clinical, and basic research studies can be directed and justified, in order to pursue causal mechanisms and suggest more effective interventions.

Applying Selected Conditions as Indicators of Clinical Harm Reduction

Some of the conditions reviewed in this chapter may be applied as indicators of the general biological effects of new tobacco products. For example, cigarette smoking has been consistently found to be an independent risk factor for an adverse clinical course of both peptic ulcer disease and wound healing. The effects of smoking on ulcer formation and healing have been clearly described clinically and in animal models. Peptic ulcers have been found to be larger, slower to heal, and more likely to recur among smokers and to exhibit clinically improved healing upon cessation. Surgical and traumatic wounds heal more slowly in cigarette smokers. The committee recommends that rigorous clinical studies be designed and executed to determine whether variations in ulcer and wound healing rates are related to different categories of tobacco products, including those with claims of harm reduction. This may offer the opportunity to define

There has been a push from the public health community to force cigarette manufacturers to modify cigarettes to reduce their combustibility (Chapman, 1999). In response to pressure from various organizations to decrease the danger of improperly discarded cigarettes, the Cigarette Safety Act of 1984 was signed. This act created the Technical Study Group in 1987 to study the technical and commercial feasibility of developing a fire-safe cigarette. This group was comprised of representatives of different medical organizations, federal agencies, the furniture industry, fire service, and four of the top tobacco companies (Barillo et al., 2000). The report of this group stated that it was technically and commercially feasible to develop fire-safe cigarettes and that a reduction of up to 90% in morbidity and mortality could be reached if such modifications were made (Achauer and McGuire, 1989). The main characteristics of cigarettes that were found to significantly decrease flammability included decreased packing density, smaller cigarette circumference, decreased paper porosity, and reduction of citrate—a paper-burning additive (Achauer and McGuire, 1989). The Fire Safe Act was passed in 1990 and mandated further study of the issue based on the recommendations of the Technical Study Group. The Technical Advisory Group was formed which developed cigarette fire-safety test methods. No federal legislation has been passed up to this time that has set a fire-safety standard for cigarettes. In June 2000, however, the state of New York passed a cigarette fire-safety bill that would require all cigarettes sold in New York to meet flammability standards by 2003 (Perez-Pena, 2000).

PARKINSON'S DISEASE

Parkinson's disease is a neurological disease affecting 1–2% of the population that is characterized by motor dysfunction and, in severe cases, cognitive dysfunction caused by loss of dopamine and other neurotransmitters through the destruction of neurons in the substantia nigra. Over the last decade there have been many epidemiological studies suggesting a biologically protective effect of cigarette smoking on the risk of Parkinson's disease. Numerous population based case-control and prospective studies have indicated an inverse dose–response relationship between smoking and Parkinson's disease (Gorell et al., 1999; Tzourio et al., 1997; Grandinetti et al., 1994; Checkoway and Nelson, 1999). In a large 26-year prospective follow-up of the Honolulu Heart Study, Grandinetti et al. (1994) found the relative risk of Parkinson's disease among smokers to be 0.39 with a dose–response relation to pack-years of smoking. Postulated mechanisms of the neuroprotective traits of smoking include direct neuronal effects of nicotine on dopamine release in the substantia nigra, reduction of the action of monoamine oxidase B, or reduction of free radical injury (Grandinetti et al., 1994; Kelton et al., 2000; Checkoway et al., 1998; Court et al., 1998). Critics of the protective association between smoking and Parkinson's disease have attributed the results to an artifact of selective mortality of smokers that would have acquired Parkinson's, diagnostic errors, cause-and-effect bias, or another unrecognized confounder (Morens et al., 1996; Riggs, 1996).

PREECLAMPSIA

Studies have described an inverse relationship between cigarette smoking and the risk of preeclampsia. Many studies have reported around a 30–70% decrease in risk for preeclampsia among smokers, using reported daily cigarette use and serum cotinine levels, when compared to nonsmokers. A finding of a dose–response effect has been less consistent (Klonoff-Cohen et al., 1993; Lain et al., 1999; Lindqvist and Marsal, 1999; reviewed in Conde-Agudelo et al., 1999). A population-based study by Cnattingius and colleagues (1997) found a decreased incidence of

baseline BMI, age, physical activity, genetic predisposition, and so forth (reviewed in Froom et al., 1998; Pomerleau et al., 2000; Williamson et al., 1991; O'Hara et al., 1998).

The physiologic effect of nicotine has been described as a combination of a reduction in caloric intake and an increase in caloric expenditure. Although the evidence has been inconsistent, short-term increases in intake postcessation occur, peaking within weeks or months (Froom et al., 1998), and decreases in intake upon relapse or initiation have been noted. The research has supported acute changes in metabolic rate associated with changes in smoking, but chronic changes have not been as well supported. A further hypothesis for the weight change seen with change in smoking habits is the speculation that cigarette smoke or nicotine changes the weight set point of the smoker (reviewed in Perkins, 1993).

Investigators have found that weight changes upon smoking initiation and cessation are nicotine associated (Emont and Cummings, 1987; Grunberg et al., 1986). Consistent with many previous studies, Doherty et al. (1996) found that nicotine replacement during smoking cessation suppresses weight gain. In their randomized control study, they describe a linear relationship between nicotine dose and postcessation weight gain, with placebo users gaining the most weight. This relationship was maintained when smoking was biochemically validated by serum cotinine.

DRUG INTERACTIONS

Exposure to cigarette smoke affects the metabolism of many categories of drugs, which may make the action of a certain dose of a drug unpredictable. Certain constituents of tobacco smoke can affect drug action through pharmacokinetic (changes in absorption, distribution, metabolism, and elimination) and pharmacodynamic (changes in drug action or response) actions (Schein, 1995). Among the best-understood agents that affect enzymes of drug metabolism are polycyclic aromatic hydrocarbons (PAHs) and nicotine—though less defined—selectively induces various cytochrome P-450 (CYP) enzymes and uridine 5-diphosphate (UDP) glucuronosyltransferases, while carbon monoxide and heavy-metal constituents have been found to inhibit or decrease certain CYP enzymes (Zevin and Benowitz, 1999).

The effect of cigarette smoke exposure on drug metabolism can influence the action of many commonly used drugs, including certain anitidepressants, antipsychotics, heart medications such as β-blockers and antiarrhythmics, anticoagulants, alcohol, caffeine, theophylline, and others (D'Arcy, 1984; Schein, 1995; Zevin and Benowitz, 1999). Many of the drug interactions are of unknown clinical significance, but others may necessitate the adjustment of medication dose among smokers.

Although not considered to be due to an interaction of cigarette smoke and oral contraceptive pills, it is important to note the significantly increased risk of cardiovascular and cerebrovascular events in female smokers using oral contraceptives.

FIRE SAFETY

Cigarettes are the leading cause of accidental fires in the United States, causing about 20–25% of all fire deaths and resulting in about 1,000 deaths and 2,500 injuries annually (Brigham and McGuire, 1995; Barillo et al., 2000). Often, fires are caused by the ignition of upholstered furniture and mattresses by lit cigarettes (Achauer and McGuire, 1989). Many fires also involve the use of alcohol by the smoker (Botkin, 1988). The fire hazard of cigarettes stems from the fact that a cigarette continues to burn until completely consumed.

SCHIZOPHRENIA

It has been reported that up to 80% of patients with schizophrenia smoke cigarettes (Simpson et al., 1999; McCreadie and Kelly, 2000). The rate of smoking among schizophrenics is also higher than rates among other mentally ill patients (Leonard et al., 2000; Tidey et al., 1999). Many different reasons for the high rate of smoking among schizophrenics have been postulated including "self-medication" of the symptoms of schizophrenia, attenuation of the adverse effects of antipsychotic medication, social factors of schizophrenic patients that predispose them to smoke, or genetic vulnerability for both conditions (reviewed in Levin and Rezvani, 2000; Tidey et al., 1999). Nicotine may attenuate the negative symptoms of schizophrenia by stimulating the release of dopamine and glutamate (Dursun and Kutcher, 1999). Nicotine has also been found to stabilize sensory deficits found in schizophrenia including smooth eye tracking movements and auditory gating, possibly through decreased expression of the α-7 nicotinic acetylcholine receptor (Leonard et al., 2000; Durson and Kutcher, 1999). Furthermore, cigarette smoking has been found to reduce monoamine oxidase activity, which is thought to increase vulnerability to the development of schizophrenia (Simpson et al., 1999; Fowler et al., 1996).

DEPRESSION

Depression has consistently been linked with smoking (Glassman, 1993; Breslau and Johnson, 2000). Studies have demonstrated that a history of major depression is associated with a greater prevalence of smoking and less success in smoking cessation (Kinnunen et al., 1996; Anda et al., 1990; Balfour and Ridley, 2000). Kinnunen and colleagues, looking at data from a randomized interventional trial, found that significantly fewer depressed smokers were able to remain abstinent 3 months after cessation compared to nondepressed smokers. The same study concluded that depressed patients were more responsive to the use of nicotine for cessation. Investigators have suggested that depressive symptoms may be a part of the withdrawal syndrome in those with a history of depression, presenting an obstacle to successful cessation (Glassman et al.). It has also been proposed that depression increases the intensity of nicotine dependence (Breslau et al., 1998; Carton et al., 1994). A prospective study by Breslau and colleagues (1998) with a 5-year follow-up found that baseline major depression tripled the risk for progression to daily smoking. Smokers with a history of depression or depressive symptoms are thought to "self-medicate" with nicotine and its antidepressant properties (Carton et al., 1994; Lerman et al., 1996). Other studies have hypothesized that smokers are predisposed to develop depression secondary to chronic nicotine central nervous system (CNS) effects. Investigators have suggested that certain genetic or environmental factors may predispose patients to depression and the tendency to smoke independently (reviewed in Breslau et al., 1998).

WEIGHT CHANGE

Weight loss is a commonly cited reason for smoking, especially among young females (reviewed in Perkins, 1993), and fear of weight gain has been an obstacle to successful cessation (Froom et al., 1998; Emont and Cummings, 1987). It has been reported that around 80% of smokers gain weight after cessation (Perkins, 1993). The average weight gain after smoking cessation is 3–4 kg. This weight gain has been found to peak within the first few weeks or months of cessation, and smokers often return to the weight range of nonsmokers. A recent large prospective study, however, found that significant weight gain continued 5 years after cessation (O'Hara et al., 1998). The amount of weight gain, however, is subject to many individual differences in

DIABETES

Several studies over the last decade have indicated a positive dose-related association between cigarette smoking and risk of non-insulin dependent diabetes mellitus (NIDDM) (Uchimoto et al., 1999; Rimm et al., 1993; Simon et al., 1997; Nakanishi et al., 2000; Rimm et al., 1995). In a Nurses' Health Study cohort, Rimm et al. (1993) found a positive, dose-related association between cigarette smoking and development of NIDDM that persisted after controlling for age, body mass index (BMI), family history, physical activity, alcohol, and so forth. Simon et al., (1997), in another large prospective study, found a significant link between smoking and increased waist-to-hip ratios and an odds ratio of 1.38 for the relationship of smoking more than 10 cigarettes per day and the prevalence of reported diabetes mellitus. The odds ratio was modified when data were adjusted for waist-to-hip ratio, suggesting a relationship between smoking-associated body fat distribution and the occurrence of diabetes. Investigators have consistently suggested that smoking is an independent risk factor for increased insulin resistance, measured by insulin clamp test and oral glucose challenge, among both diabetics and nondiabetics (Facchini et al., 1992; Targher et al., 1997), and increased transient blood glucose levels during oral and intravenous glucose tolerance tests (Janzon et al., 1983). Muhlhauser (1994) in his review of smoking and diabetes discusses the epidemiological evidence suggesting increased risk of diabetic nephropathy and retinopathy and increased overall mortality among smokers.

RENAL DISEASE

Smoking has been linked to abnormal renal function in diabetics and more recently in nondiabetics (Cirillo et al., 1998; Ritz et al., 2000; Pinto-Sietsma et al., 2000; Halimi et al., 2000). Research has consistently established the association of cigarette smoking with a two- to threefold increased risk of microalbuminuria and proteinuria and an increased rate of progression to diabetic nephropathy and ultimately end-stage renal disease in type I and type II diabetics in a dose-responsive manner (reviewed in Orth, 2000; Ritz et al., 2000). Other studies have found an independent association of smoking with increased risk of developing renal failure in patients with autosomal dependent polycystic kidney disease, lupus nephritis, and glomeruloephritis (Ritz et al., 2000).

Recently, consistent with previous findings, in a cross-sectional study of nondiabetic patients by Pinto-Sietsma and colleagues (2000), current smokers were found to have a dose-responsive increased rate of high-normal albuminuria and microalbuminuria (markers of some degree of renal damage). Current smokers also had significantly abnormal glomerular filtration rates (increased or decreased) compared to nonsmokers. Former smokers had a risk for both events that fell between that of current smokers and nonsmokers, suggesting some degree of reversibility of the effects of smoking. Another large population-based, cross-sectional study (Halimi et al., 2000) of subjects without known renal disease showed that current and former smokers, even after adjusting for diagnoses of diabetes and hypertension, had greater risks for proteinuria by dipstick testing compared to nonsmokers (RR = 2-3). Current male smokers in this study also had a higher creatinine clearance than nonsmokers, suggesting a degree of glomerular hyperfiltration.

Many mechanisms of smoking-attributable nephrotoxicity have been postulated including increased sympathetic nervous system activity, transient blood pressure elevation, endothelial cell damage and dysfunction of renal vasculature, direct toxic effects on tublar cells, and oxidative stress (Pinto-Sietsma et al., 2000; Orth, 2000).

vasoconstrictive effects of nicotine that prevent revascularization of healing bone, and decreased body weight due to smoking, which is an independent risk factor for osteoporosis.

OCULAR DISEASE

Cigarette smoking has been associated with numerous diseases of the eye. Smoking can induce tobacco smoke-mediated vasoconstriction, atherosclerosis, hyperviscosity, hypercoagueability, and decreased oxygen availability in ocular tissues. There is a strong association with ischemic diseases including amaurosis fugax, retinal infarction, and anterior ischemic optic neuropathy (Solberg et al., 1998). Smoking has also been consistently associated with two of the most important causes of vision loss, cataracts and age-related macular degeneration. A dose-dependent relationship between cigarette smoking and risk and severity of cataracts has been established (Hankinson et al., 1992; West et al., 1995). A large prospective study by Delcourt et al. (2000) found an OR of 1.9 for nuclear-type cataracts in current smokers and a two- to fourfold increase in the rate of cataract surgery among current and former smokers. Most studies have found the increased risk limited to nuclear-type cataracts, although there has been evidence of an increased risk of posterior subscapular cataracts as well (Solberg et al., 1998). The risk of cataract formation among smokers appears to be related to lifetime cumulative cigarette dose, with less reduction in risk found among heavy smokers compared to moderate and light smokers after cessation (Christen et al., 2000; Hankinson et al., 1992). The mechanism of smoking-associated cataract formation is thought to be due to direct and indirect oxidative damage to the lens and exposure to heavy metals in tobacco smoke.

Age-related macular degeneration induced by free-radical formation and oxidative stress associated with cigarette smoking has also been well supported in the literature. Many studies have found a two- to threefold increase in risk of macular degeneration among smokers (reviewed in Solberg et al., 1998).

DERMATOLOGIC CONDITIONS

In many retrospective and prospective studies, cigarette smoking has been associated with premature wrinkling independent of age, sun exposure, pigmentation, and sex (Smith and Fenske, 1996; Ernster et al., 1995). Kadunce et al (1991) found a dose–response relationship associated with pack-years of exposure. Smokers with a 0.9 to 49 pack-year history were twice as likely to be wrinkled compared to nonsmokers. The risk increased to 4.7 among 50+ pack-year smokers. Tobacco smoke toxins are believed to have a detrimental effect on collagen and elastin integrity and on the microvasculature of skin, to increase oxidant stress free-radical activity, and to have possible antiestrogenic effects (Kadunce et al., 1991; Smith and Fenske, 1996; Leow and Maibach, 1998; reviewed in Frances, 1998).

Psoriasis also has been found to be associated with cigarette smoking, especially in women (Poikolainen et al., 1994; Naldi et al., 1999; Mills et al., 1992). A recent case-control study by Naldi et al. (1999) found an OR of 1.5–2.4 among smokers and exhibition of a dose–response relationship.

A few studies have also suggested a positive association of cigarette smoking with a variety of dermatological changes such as psoriasis palmoplantar pustulosis, atopic dermatitis, and yellowing of fingers and nails (reviewed in Smith and Fenske, 1996). These findings are not discussed in detail here.

spective study of British doctors, Doll et al. (2000) found no significant association of current or former smoking with the risk of Alzheimer's disease or other types of dementia including vascular dementia. In another large prospective study (the Rotterdam study) by Ott et al. (1998), it was found that smoking significantly increased the risk of vascular and Alzheimer's dementia and was linked to a younger age of onset. Smokers with the apolipoprotein-E4 (APOE4) allele have shown a reduction in dementia risk, consistent with many other studies (Merchant et al., 1999; Ott et al., 1998; Carmelli et al., 1999). The association persisted when factors such as educational status, alcohol use, and ethnicity were controlled.

Nicotine, however, has been shown to have beneficial effects on cognition in human and animal studies. Evidence exists to suggest that nicotinic cholinergic receptors are decreased in Alzheimer's patients, and the receptors have been found to increase with chronic exposure to nicotine. Nicotine has also been found to decrease neuron loss in animal models of Alzheimer's disease (reviewed in Lee, 1994). Nicotine has been shown to acutely ameliorate recall, attentional, and visuospatial abilities (Leibovici et al., 1999; Newhouse et al., 1997) and to improve performance of memory-related tasks in animal studies (Buccafusco et al., 1999; Newhouse et al., 1997).

Attempting to reconcile the contradictory studies, investigators have postulated numerous reasons for the inconsistent findings. Investigators have raised the possibility that the protective effect of smoking in Alzheimer's disease (AD) may be mediated by the APOE4 allele (Ott et al., 1998; Van Duijn et al., 1995). Many of the earlier studies that pointed to a negative relationship between smoking and AD were case-control designs in which it is necessary to match cases and controls by age and other variables. In this design, there may be an increased effect of selective mortality among smokers, thus decreasing the proportion of smokers available (Debanne et al., 2000; Riggs, 1993). In addition to selection bias, other sources of bias that may have been a factor in the early studies include problems inherent in the design of retrospective studies such as recall bias and the use of surrogate informants for case patients (Doll et al., 2000) and, generally, poor control of confounding variables.

ORTHOPEDIC CONSEQUENCES

Cigarette smoking has been linked to adverse orthopedic consequences including osteoporosis, hip fracture, and delay in bone healing. A dose–response effect has been reported for the increased risk of hip fracture and decreased bone mineral density (BMD) in many but not all studies (Cornuz et al., 1999; Vecchia et al., 1991; Hollenbach et al., 1993; Hoidrup et al., 1999). Based on a meta-analysis by Law and Hackshaw (1997), one out of eight hip fractures is attributable to smoking. Smoking is associated with loss of bone mineral density, and this association increases with age especially in postmenopausal women. The study goes on to conclude that the risk of hip fracture is 17% greater in smokers at age 60, 41% greater at age 70, 71% greater at age 80, and 108% greater at age 90. Reversal of the risk for hip fractures has been described 10–20 years postcessation (Vecchia et al., 1991; Cornuz et al. 1999). There have been few studies examining BMD and hip fracture risk among male smokers. An evaluation of the National Health and Nutrition Examination Survey (NHANES) I Epidemiologic Follow-up Study found a nonsignificant increased risk associated with smoking (Mussolino et al., 1998). A review by Kwiatkowski et al. (1996) stated that bone mineral content of smokers was 10–20% lower among men and 20–30% lower among women. Hypothesized mechanisms include impairment of osteoblastic function and consequently decreased bone formation, reduced calcium absorption,

closely associated with seropositive RA compared to rheumatoid factor (RF) negative disease (Silman et al., 1996). Evidence of a dose–response relationship has not been consistently upheld. It is unclear whether smoking plays a causal role in the etiology or progression of rheumatoid arthritis or the formation of rheumatoid factor or whether it is linked to other unidentified factors that predispose patients to RA.

ORAL DISEASE

Research has consistently found that cigarette smoking is a major risk factor for periodontal disease (Tomar and Asma, 2000); studies report 30–75% of periodontitis linked to cigarette smoking. Smoking has been linked to increased frequency of diseased sites, reduced periodontal height, and a weak association with gingival bleeding (Bergstrom, 2000). A dose-related relationship has been described. In a review by Haber (1994), he noted that smokers had earlier onset of disease, resistance to treatment, and faster disease progression. Smoking cessation has been found to improve gingival health, and there is evidence of a decrease but not a complete reversal in the severity and prevalence of periodontitis among former smokers. Hypothesized mechanisms of action include smoking-induced impairment of immunity, reduced epithelial cell and fibroblast function involved in the healing process, decreased bone mineralization, and local nicotine-mediated gingival vasoconstriction leading to decreased blood flow and tissue oxygen delivery (Palmer et al., 1999; Haber, 1994; Christen, 1992).

Increased risk of oral lesions in immunocompromised smokers has been described. These lesions include hairy leukoplakia, oral candidiasis, and human papillomavirus (HPV) lesions; on the other hand, smoking has been consistently found to decrease the risk of aphthous ulcers (Palacio et al., 1997).

Smokeless tobacco use has been extensively linked to oral disease. The prevalence of leukoplakia, a white mucosal plaque that cannot be attributed to any other disease process, among smokeless tobacco users is very high (at least 50% by some reports), and it is generally accepted that smokeless tobacco use is an important cause (Spangler and Salisbury, 1995). The site of plaque formation in smokeless tobacco users corresponds to tobacco contact with the mucosa. The prevalence of tobacco-associated leukoplakia exhibits a dose–response relationship, and there has been evidence of reversal of these changes upon cessation of tobacco use (Grady et al., 1990). A review by Walsh and Epstein (2000) found the rate of malignant transformation of tobacco-attributable leukoplakia to range between 4 and 17.5%.

The dentitia and gingiva adjacent to the location of tobacco placement in the mouth are at a high risk of oral problems ranging from gingivitis and gingival recession to halitosis (Spangler and Salisbury, 1995). A study involving professional baseball players by Robertson et al. (1990) found that the only significant periodontal changes associated with smokeless tobacco use are gingival recession, loss of gingival attachment, and mucosal lesions at the area of tobacco placement. The evidence has been uncompelling regarding the risk of dental caries and gingivitis among smokeless tobacco users (Walsh and Epstein, 2000).

DEMENTIA

Many previous studies have suggested an inverse relationship between smoking and Alzheimer's dementia (Brenner et al., 1993; Forbes and Hayward, 1993; reviewed in Lee 1994). More recent studies, however, have suggested no relationship or possibly a positive association (Merchant et al., 1999; Doll et al., 2000; Ott et al., 1998; Debanne et al., 2000). In a large pro-

SURGICAL WOUND HEALING

Cigarette smoking and its adverse effects on wound healing have been well established in animal models and in surgical patients (Mosely et al., 1978). Surgical complications experienced by smokers include increased failures of amputations, skin flaps, and atrioventricular (AV) shunts (Kwaiatkowski et al., 1996). Mechanisms suggested for the adverse effects on wound healing include the cutaneous vasoconstrictive properties of nicotine, poor oxygen delivery due to an increase in carboxyhemoglobin levels leading to cellular hypoxia and tissue ischemia, and possibly interference with cellular respiration and metabolism due to hydrogen cyanide (HCN) (Kwaiatkowski et al., 1996; Silverstein, 1992; Campanile et al., 1998; Jensen, 1991). Further detrimental effects on wound healing attributed to smoking are decreased microcirculation due to increased platelet aggregation and microclot formation and reduction of epithelial cells, fibroblasts, and macrophages, which are important in scar formation (Silverstein, 1992; Campanile et al., 1998).

INFLAMMATORY BOWEL DISEASE

Smokers with Crohn's disease, especially women, have increased risk of developing severe disease and have a greater risk of requiring surgery and of having postsurgical complications (Thomas et al., 2000). Studies, reviewed by Rhodes and Thomas (1994), have attributed a three- to fivefold higher risk of developing Crohn's disease to smoking. Ex-smokers were found to have less risk, and nonsmokers or those who had quit for at least 10 years were found to experience the least risk. Several studies have found a decrease in the need for surgery after smoking cessation and a decrease in recurrence after surgery (Cosnes et al., 1996; Yamamoto and Keighly, 2000).

In contrast, smoking has been shown to have a protective effect for ulcerative colitis (UC), with odds ratios (ORs) between 0.34 and 0.48, and smokers with UC exhibit a better clinical course (reviewed by Calkins et al., 1989). The literature indicates a negative association (pooled OR = 0.41) of current smoking with the development of ulcerative colitis, a significant positive association among ex-smokers, and a positive or equivocal risk among nonsmokers (Thomas et al., 2000). Researchers have found a positive influence of smoking on the clinical course of UC, with a lower rate of recurrence found among smokers (Fraga et al., 1997). Studies have revealed an earlier age of onset of ulcerative colitis in lifetime nonsmokers, and among a sample of patients who quit smoking, almost 70% developed UC during the first year postcessation (reviewed in Thomas et al., 1998; Rhodes and Thomas, 1994). The pathological process is involved in the relationship between smoking and inflammatory bowel disease is unknown. It is speculated that nicotine affects cellular immunity, especially the levels of immunoglobulin A (IgA) that are important in the defense of mucosal tissue (Rhodes and Thomas, 1994). It is also postulated that nicotine is involved in the reduction of blood flow and ischemic changes that may contribute to the changes seen in Crohn's disease.

RHEUMATOID ARTHRITIS

Environmental risk factors are known to be important in the pathogenesis of rheumatoid arthritis (RA). The few studies that have been evaluated smoking as a risk factor indicate a positive link between cigarette smoking and the development of rheumatoid arthritis (Uhlig et al., 1999). This relationship has been identified among men (Heliovaara et al., 1993), with a more modest association found among women smokers (Karlson et al., 1999). Smoking has also been more

16

Other Health Effects

This chapter briefly reviews some of the health outcomes of tobacco consumption not covered in previous chapters. Although these outcomes by themselves are not as prevalent or threatening as cardiovascular disease, respiratory disease, or cancer, they do contribute significantly to the morbidity and reduced quality of life associated with smoking. In addition, cigarette smoking is associated with a small number of positive health outcomes in Parkinson's disease, ulcerative colitis, and preeclampsia, which are reviewed here. This is not intended to be an exhaustive review of smoking-attributable disease but does include peptic ulcer disease, wound healing, inflammatory bowel disease, rheumatoid arthritis, oral disease, dementia, osteoporosis, ocular disease, diabetes, dermatological disease, schizophrenia, and depression.

PEPTIC ULCERS

Cigarette smokers have been found to have an increased risk of peptic ulcer disease, increased rate of relapse after treatment, and increased risk of the complications associated with ulcer development (Smedley et al., 1988; Kato et al., 1992). A prospective study by Kato et al. (1992) is consistent with previous findings suggesting a positive association between cigarette smoking and gastric and duodenal ulcers, with relative risks (RR) of 3.4 and 3.0, respectively. This association was maintained after controlling for alcohol use. Ma et al. (1998) reviewed potential mechanisms of the effect of smoking on ulcer formation and healing. These mechanisms include increased levels of oxygen-derived free radicals, which are known to injure gastric mucosa; decreased mucosal blood flow mediated by decreased levels of nitric oxide (NO; a potent vasodilator); increased neutrophil infiltration; reduced epithelial cell proliferation and granulation tissue formation; and decreased prostaglandin synthesis. Ma and his colleagues (1999) demonstrated grossly the slowing of ulcer healing and an increase in ulcer size associated with smoking in rat models, which were attributed to reduced blood flow at the ulcer margins and decreased constitutive NO synthesis. Cigarette smoking has also been found to augment nonsteroidal anti-inflammatory drug (NSAID) and alcohol-attributable peptic ulcer disease (Ma et al., 1998; Guo et al., 1999).

Ulcer healing has been found to improve with cessation and reduction of smoking. Presenting results consistent with many other studies, Tatsuta et al. (1987) described the course of healing of patients who were advised to reduce their smoking (by at least 50%) or to stop. They found that after 12 weeks of treatment, 91.7% of the ulcers had healed in patients who reduced or stopped smoking, while only 25% had healed in patients who continued to smoke. Furthermore, about 23% of ulcers recurred in patients who stopped or reduced their smoking during the 6-month follow-up, while 75% recurred in those who continued to smoke.